Spirometric patterns in young and middle-aged adults: a 20-year European study

Spirometric patterns in young and middle aged adults. A 20-year European study

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ABSTRACT

Background

Understanding the natural history of abnormal spirometric patterns at different stages of life is critical to identify and optimize preventive strategies. We aimed to describe characteristics and risk factors of restrictive and obstructive spirometric patterns occurring before 40 years (young onset) and between 40 and 61 years (mid-adult onset).

Methods

We used data from the population-based cohort of the European Community Respiratory Health Survey (ECRHS). Pre-bronchodilator FEV_1 and FVC were assessed longitudinally at baseline (ECRHS1, 1993-1994) and again 20-years later (ECRHS3, 2010-2013). Spirometry patterns were defined as: restrictive if $FEV_1/FVC \geq LLN$ and $FVC < 10^{th}$ percentile, obstructive if $FEV_1/FVC < LLN$, or normal otherwise. Five spirometry patterns were derived depending on whether participants never developed restrictive/obstructive (normal), developed restrictive/obstructive at baseline (young-onset) or at last follow-up (mid-adult onset). Characteristics and risk factors associated with these patterns were described and assessed using multi-level multinomial logistic regression analysis adjusting for age, sex, sample (random or symptomatic) and centre.

Results

Among 3502 participants (mean age=30·4 [SD 5.4] at ECRHS1, 50·4 [SD 5.4] at ECRHS3), 2293 (65%) had a normal, 371 (11%) a young restrictive, 301 (9%) a young obstructive, 187 (5%) a mid-adult onset restrictive, and 350 (10%) a mid-adult onset obstructive spirometric pattern. Being lean/underweight in childhood and young adult-life was associated with the occurrence of the young spirometric restrictive pattern (RRR=1·61 95% confidence interval (CI)=1·21-2·14, and RRR=2·43 95%CI=1·80-3·29; respectively), so were respiratory infections before 5 years (RRR=1·48, 95%CI=1·05-2·08). Main determinants for young obstructive, mid-adult restrictive, and mid-adult obstructive patterns were asthma, obesity, and smoking, respectively.

Conclusion

Spirometric patterns with onset in young and mid-adult life were associated with distinct characteristics and risk factors.

Take home message

What is already known on this topic

Abnormal spirometric restrictive and obstructive patterns occurring throughout a life course are likely resulting from different trajectories of lung function growth and decline. Risk factors vary between restrictive and obstructive patterns.

What this study adds

Characteristics and risk factors for restrictive and obstructive spirometric patterns differ profoundly based on whether their onset occurs in young versus mid-adult life.

How this study might affect research, practice or policy

These differences in relation to the onset of spirometric patterns should be taken into account by future studies addressing possible prevention and treatment strategies of abnormal spirometric patterns.

INTRODUCTION

Lung function impairment, detected by spirometry, can be classified into two main abnormal phenotypes: the obstructive pattern (defined by reduced levels of the ratio of Forced Expiratory Volume in 1 sec (FEV_1) to the Forced Vital Capacity (FVC)) and the restrictive spirometric pattern, also referred to as Preserved Ratio Impaired Spirometry (PRISm)[1] (characterized by reduced levels of both FEV_1 and FVC, while FEV_1/FVC remains within normal ranges).[2, 3] The obstructive pattern has been extensively studied and is routinely diagnosed in current practice, whereas the restrictive spirometric pattern has been under-recognized despite being prevalent and associated with higher morbidity and mortality, reduced physical activity and worse quality of life compared to normal pattern.[2-8]

Recent studies have conclusively shown that the obstructive pattern can develop in adult life through two main trajectories: one characterized by an accelerated decline of FEV_1 and FEV_1/FVC in adulthood, after lung function reached its peak by young adult life; the other by lung function deficits that are already established in young adulthood, before entering the declining phase.[9-11] Little is known on whether spirometric restriction also develops following distinct trajectories, especially FVC trajectories. A recent study has shown that a low FVC trajectory that starts low from early life is associated with true restriction at age 45 years as measured by complex lung function measures[12]. However, this study did not use the above standard definition of restrictive spirometry pattern in its longitudinal analysis.

Using data from a longitudinal European cohort, we aimed to describe characteristics and risk factors of both restrictive and obstructive spirometric patterns occurring before 40 years (young onset) and after 40 years (mid-adult onset). Understanding the natural history and risk factors associated with these patterns can lead to identify possible preventive strategies and time windows in life when these strategies can be most effective.

MATERIAL AND METHODS

Study Design

The European Community Respiratory Health Study (ECRHS) has been described elsewhere.[13] Briefly, ECRHS is a multi-centre cohort involving 46 centres in 25 countries, across Europe and Australia. Between 1991-1993, participants aged 20 to 44 years were

randomly selected from the population and complemented with a sample of subjects with asthma-related symptoms (ECRHS1). Two follow-up surveys took place approximately 10 years (ECRHS2) and 20 years (ECRHS3) later. All participants answered a detailed questionnaire and underwent a clinical visit at each occasion, where spirometry and blood sample collection were performed. Overall, the response rate at the last follow-up was 53%.[14]

The current study used longitudinal data collected at baseline (ECRHS1) and at the last follow-up (ECRHS3). Only participants aged < 40 years at baseline and participants aged ≥ 40 at the last follow-up were included in this study in order to have complete separation between spirometric patterns assessed in "young" (ECRHS1, age 20 to 39) and "mid-adult" (ECRHS3, aged 40 to 61) life (Figure 1).

Written informed consent was obtained from all participants and, in each participating centre, the study was approved by the appropriate institutional ethics committees.

Lung function measurement

Pre-bronchodilator lung function was used to determine spirometric patterns at each survey. Measurements reproducible within 150mL from at least two of a maximum of five correct manoeuvers were included, following the American Thoracic Society (ATS) recommendations.[15] Details of the spirometers used in each centre are provided elsewhere.[16] Since 2005 the ATS and the European Respiratory Society have recommended the use of lower limit of normal (LLN) for FEV_1/FVC to define airway obstruction in epidemiological studies.[17] In contrast, no consensus exists on how to define spirometric restriction[18], although some studies[19] have used definitions based on the lowest 10^{th} percentile of FVC to maximize sample size. Previously used ECRHS-specific equations[7] were used to calculate the LLN for FEV_1/FVC and the 10^{th} percentile for FVC. The *a-priori* spirometric patterns were then defined as:

- Normal spirometry if $FEV_1/FVC \geq LLN$ and $FVC \geq 10^{th}$ percentile both at baseline and follow-up
- Young onset restrictive spirometric pattern if $FEV_1/FVC \geq LLN$ and $FVC < 10^{th}$ percentile at baseline
- Young onset obstructive spirometric pattern if $FEV_1/FVC < LLN$ at baseline

- Mid-adult onset restrictive spirometric pattern if $FEV_1/FVC \geq LLN$ and FVC < 10th percentile at follow-up, while being normal at baseline
- Mid-adult onset obstructive spirometric pattern if $FEV_1/FVC < LLN$ at follow-up, while being normal at baseline.

Characteristics and risk factors collected at baseline (ECRHS1)

Early life risk factors, reported by the participants at ECRHS1, included the following parental, infancy, and childhood factors: maternal/paternal asthma, parental education, maternal age at birth, maternal smoking in pregnancy, parental smoking, history of respiratory infections before 5 years, childhood asthma, living in city or rural place during childhood.

Young adult risk factors referred to characteristics assessed at ECRHS1 when participants were 20 to 39-yrs old and included: smoking status and pack-years, asthma in the last 12 months (defined as ever had asthma plus any of the following occurring in the last 12 months: use of asthma medication, having asthma attack or having had shortness of breath), atopy (any positive specific IgE (cat, house dust mite, grass) >0.35 ug/ml), and Body Mass Index (BMI). BMI was categorized into low (<20 kg/m^2), normal (20 to <25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (≥ 30 kg/m^2).[20]

Change between ECRHS1 and ECRHS3

BMI, smoking status and pack-years were available both at ECRHS1 and ECRHS3. Longitudinal categories of BMI were classified as persistent underweight, persistent normal, persistent overweight, underweight to normal, underweight/normal to overweight/obesity and a decrease in BMI. Because only 68 participants had a BMI category in ECRHS1 greater than their BMI category in ECRHS3, they were all included in the "decrease in BMI category" group. Longitudinal categories of smoking were classified as never, ex-smokers (if they were smokers before ECRHS1), quitters (if they quitted between ECRHS1 and ECRHS3) and late starters (if they started after ECRHS1).

Participant characteristics collected at ECRHS3

Additionally, at ECRHS3, participants were asked about their body silhouettes at age 8, the time of puberty and age 30. This tool has been previously validated[21] in this cohort. Among the 9 body silhouettes (from scale 1 (extremely lean) to scale 9 (extremely obese)),

participants were asked to tick the figural scale that best described their body silhouette at that age. This scale was then categorised into 4 groups in order to have sufficient numbers in each group and according to the best trade-off for obesity definition[21] (category 1: lean, 2 to 3: normal, 4: overweight, 5 to 9: obese). Longitudinal categories for changes in body silhouette between the ages of 8 and 30 years were also generated, with methods similar to those described for the longitudinal categories of BMI.

Participants' characteristics evaluated at ECRHS3 were chronic conditions (diagnosis of chronic bronchitis, heart disease, hypertension, stroke, diabetes, depression and ankylosing spondylitis or psoriatic arthritis), dyspnea, body composition (fat-mass and fat-free mass, derived from bioelectrical impedance analysis using validated equations[22]) and physical activity. Z-score for fat-mass and fat-free-mass were standardised on sex, height and height-squared. Low, normal and high categories were further derived according to 10^{th} percentiles. Lowest tertile of total Mets-min per week[23] was used to describe physical activity levels.

Statistical analysis

Adjusted mean levels of FEV_1, FVC and FEV_1/FVC over age were graphically represented after estimating margins from 3-levels (level 1: visit, level 2: participant, level 3: centre) mixed models with lung function as the dependent variable while adjusting for age, age squared (to capture acceleration of decline over time), sex and spirometric pattern, and interactions between age*sex, spirometric pattern*age, spirometric pattern*age-squared. We complemented these figures by providing figures of unadjusted mean lung function levels by survey and sex according to spirometric patterns (supplemental Figure 1).

The two groups of potential risk factors ("early-life" and "young adult-life", as described above) for the spirometric patterns were considered in the analysis. Associations between spirometric patterns and subject characteristics (at ECRHS3) as well as risk factors were first tested by bivariate analysis (chi-squared test and anova test).

For each risk factor, relative risk ratios (RRR) were estimated using 2-level multinomial logistic regressions with normal trajectory as the reference, while adjusting for age, sex, sample (to control for possible differences in risk factors and outcomes between the random and symptomatic samples) and centre (level 2, as a random effect).[24] A final multivariate

multinomial logistic regression model was also run retaining independent variables with p-value<0.1.

A series of sensitivity analyses were performed to assess the robustness of the results to assumptions about definitions and confounding. We (1) excluded participants from the symptomatic sample (n=457), (2) excluded any asthmatic at baseline (n=375), (3) used GLI equations rather than study-specific equations to define the spirometric patterns, and (4) excluded participants with an increase in FVC between ECRHS1 and ECRHS3 (n=377). All analyses were done using Stata 16 (StataCorp, Texas, USA).

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

In the present study, 3502 participants with data at both ECRHS1 (mean age=30·4, sd=5·4) and ECRHS3 (mean age= 50·4, sd=5·4) were included (Figure 1). Participants not included (lost to follow-up) were more likely to be younger, male and smoker at baseline, and to report more respiratory symptoms (supplementary Table 1). In total, 2293 (65%) had normal spirometry, 371 (11%) a young onset restrictive, 301 (9%) a young onset obstructive, 187 (5%) a mid-adult onset restrictive, and 350 (10%) a mid-adult onset obstructive spirometric patterns.

Lung function trajectories from mixed linear regression models

Mean FEV_1 levels at age 20 years were lowest among participants in both young onset restrictive and obstructive spirometric patterns and both groups followed a similar trend with FEV_1 deficits tracking over time (Figure 2a). The mean rates of FEV_1 and FVC decline during the study follow-up were 34 and 26 ml/yr respectively, but they differed substantially across spirometric pattern groups. While participants with mid-adult onset spirometric patterns (both restrictive and obstructive) had FEV_1 levels close to normal at age 20, their decline was faster than for subjects with normal spirometry. In contrast, FVC showed very similar levels and

decline for normal, young onset obstructive, and mid-adult onset obstructive spirometric patterns, while levels at age 20 were lowest for the participants with a young onset restrictive spirometry and decline was fastest for the participants with a mid-adult onset restrictive spirometry (Figure 2b). Mean FEV_1/FVC was constantly lower over age for subjects in the young onset obstructive, while a steeper decline was observed for those with mid-adult onset obstructive compared to the normal spirometry (Figure 2c). These observations were confirmed when actual unadjusted means were graphically represented according to sex (supplementary Figure 1).

Participants characteristics at follow-up

Participants in the young onset abnormal patterns were more likely to be underweight and to have a low fat-free mass Z-score at follow-up compared to the normal pattern (Table 1). 43% of those in the mid-adult restrictive pattern were obese (compared to 19% in the normal pattern). Smoking was more frequent in the mid-adult onset obstructive spirometry. Respiratory symptoms and diagnosis were more frequent in the abnormal patterns compared to normal spirometry as were cardiovascular and metabolic diseases. Ankylosing spondylitis/psoriatic arthritis was more frequent in the mid-adult onset restrictive spirometry.

Risk factors associated with spirometric trajectories

Early-life risk factors were found to be consistently related with the young onset spirometric patterns (Table 2, upper part). Maternal and paternal asthma as well as childhood asthma were most frequent among participants with young obstructive spirometry compared to normal. A positive history of respiratory infections before age 5 years was more frequent both in subjects with young onset restrictive (14%) and obstructive (18%) patterns than in subjects with the normal spirometry (10%), while the leanest silhouette at age 8 was more frequent in the young onset restrictive pattern compared to other patterns.

Among young adult risk factors (Table 2, bottom part), compared to the normal spirometry, leanest silhouette at age 30 and underweight at ECRHS1 were highest in the young onset restrictive pattern, whereas both the obese silhouettes at age 30 and obesity at ECRHS1 were highest in the mid-adult onset restrictive pattern. The proportion of underweight and obese participants were also higher in the young onset obstructive spirometry compared to normal

pattern. Cigarette smoking was the strongest risk factor for the mid-adult onset obstructive pattern, with a proportion of 71% smokers (versus 54% in the normal pattern) and a median of 12 pack-years (versus 7 pack-years in the normal pattern). Proportion of current asthma in young adult-life was remarkably higher in the young obstructive (28%) than in the normal pattern (5%) and appeared somewhat increased in the mid-adult onset obstructive (10%) pattern.

These associations were largely confirmed in multinomial models adjusted for age, sex, sample and centre (Table 3). A history of respiratory infections before age 5 was associated with both young onset patterns (RRR=1·5 and 2·0 for the young onset restrictive and obstructive pattern, respectively). Reporting the leanest silhouette at age 8 and 30 years and being underweight in young adult-life increased significantly the risk for the young onset restrictive spirometry (RRR: 1·6, 2·5, and 2·4, respectively). When these three risk factors were mutually adjusted for each other, their RRRs, particularly those for reporting the leanest silhouette at age 8 and for being underweight in young adult-life, remained consistent: 1·6, 1·9, and 2·4, respectively. Former smokers showed 32% reduced risk for the young restrictive pattern compared to the normal pattern. Atopy was associated with a 114% increased risk for the young obstructive spirometry, while participants with current asthma in young adult-life were nearly 7 times more likely to be in the young onset obstructive than the normal group.

Maternal asthma was the only early-life risk factor associated with the mid-adult onset obstructive pattern, whereas current smokers in young adult life had a 130% increased risk for developing this mid-adult onset obstructive pattern. Reporting the heaviest body silhouettes and being obese in young adult-life increased the risk of the mid-adult onset restrictive pattern (RRRs: 2·3 for both risk factors).

When we tested for possible sex differences in the association between being underweight and the young onset spirometric restrictive pattern, while the effects of having the leanest body silhouette appeared to be stronger in females than males, comparable RRRs were observed for the association between low BMI at ECRHS1 and the young onset restrictive pattern in the two sexes (see supplementary Table 2 for analyses stratified by sex). Of note, in a final analysis including all significant predictors in a single mutually adjusted model, reporting the leanest body silhouette at ages 8 and 30 as well as having low BMI at ECRHS1 remained all independently associated with the young onset restrictive spirometric pattern (supplementary Table 3).

Changes in risk factors between young and mid-adult

Table 4 shows changes and longitudinal categories of risk factors between ECRHS1 and ECRHS3 by spirometric patterns. Compared with the normal pattern, participants in the mid-adult onset restrictive pattern were more likely not only to be overweight/obese at both surveys (25% versus 32%, respectively) but also to become overweight/obese at ECRHS3 (35% versus 47%). These results were in line with those on changes in body silhouette categories between ages 8-30 years (supplementary Table 4) and with the remarkably higher increase in BMI between ECRHS1 and ECRHS3 in the mid-adult onset restrictive group (median BMI change: 4·7 [Interquartile Range:5.3]) than in any of the other patterns (medians between 2·8 and 3·0). In contrast, participants in the mid-adult onset obstructive spirometry had the highest pack-years increase ($p<0.001$), and they were about twice as likely to be persistent smokers (33%) than participants in the other spirometric patterns (16-18%). Of note, no appreciable differences in smoking were found between participants in the normal and those in the mid-adult onset restrictive spirometry.

In sensitivity analysis, estimates were mostly similar to those from the main analysis. Excluding the symptomatic sample did not change the results (supplementary Table 5). Excluding asthmatics at ECRHS1 reduced the estimates for parental and childhood asthma, while the other associations remained similar to those from main analysis (supplementary Table 6). Using GLI-equations reduced the number of individuals with abnormal spirometry (supplementary Table 7) but estimates were consistent with those observed in our main analysis. Estimates remained similar when excluding subjects with FVC value at baseline lower than FVC value at follow-up (supplementary Table 8).

DISCUSSION

This study describes the characteristics and risk factors of spirometric patterns from age 20 to 60 years in a large mostly European population. As expected by definition, we observed that young onset spirometric patterns were characterized by lung function deficits that were established by young adult-life, whereas an accelerated decline of lung function was the main

characteristic of mid-adult onset spirometric patterns. Most importantly, we found that distinct risk factors were associated with young versus mid-adult onset spirometric patterns.

Most previous studies have investigated spirometric patterns among older individuals when respiratory diseases arise more frequently but the effects of early adult deficits versus accelerated decline of lung function cannot be distinguished.[1, 7, 25] It is only recently that the full trajectories from young to older age have received more attention.[11, 26]. Our work fills the gap by contrasting the restrictive and obstructive spirometric patterns between young and mid-adult life.

On one hand, as expected, main risk factors for the young onset obstructive pattern were early life factors (parental, childhood asthma and respiratory infections before 5 years), while for the mid-adult onset obstructive pattern they were adult exposures, such as the amount of tobacco smoked. These results are very much in line with previous studies on trajectories for COPD.[9, 27] Wang et al.[27] reported parental asthma, childhood asthma and respiratory infections as risk factors for airflow limitation by young adult life. The role of early life origins as well as smoking on development of obstructive lung diseases has been widely described before.[25, 27-29]

On the other hand, the contributions of different risk factors to the trajectories of the restrictive spirometry patterns remain largely unknown. We found that reporting the leanest body silhouette in childhood and being underweight in young adult life were independently related to the young onset restrictive spirometry pattern, while on the contrary, obesity and weight-gain were strongly associated with the mid-adult onset restrictive spirometry. These results expand the growing evidence that spirometric restriction arising in young adults may be a different phenotype than the restrictive spirometry pattern observed in older adults.[30] It was particularly striking that being underweight was the most consistent risk factor for the young restrictive pattern while it had no effect among individuals with mid-adult onset spirometric restriction. This finding is in line with growing literature showing childhood underweight[19] and/or having a persistently low BMI at an early age[31] strongly predict the development of spirometric restriction in young adult life. Wang and colleagues found

underweight to be related with restrictive spirometry while early-life risk factors related to obstructive patterns.[32]

Each individual is believed to follow their own lung function trajectory which is likely influenced by a wide range of host factors and exposures starting early in life (including in utero) as well as throughout childhood and adult life after lungs have reached their full growth. It is therefore expected that different risk factors may interfere with growth or decline at different ages. This has been described in a large cross-sectional study.[30]

The reasons why individuals who are underweight in childhood and young adult-life are more likely to develop the young restrictive spirometric pattern are yet to be understood. Trajectories of low BMI from childhood into young adult-life can result from developmental growth deficits (acquired in-utero or in childhood), which have been found recently to be associated with spirometric restriction in young adults.[19] Such growth deficits may affect the lungs as well as other organs and systems, a hypothesis consistent with the increased comorbidities associated with spirometric restriction observed in this and previous studies.[1, 2, 5, 12] The early origins of young spirometric restriction are also supported by the association of this spirometric pattern with a positive report of respiratory infections in the first 5 years of life, although the possibilities of recall bias and reverse causation (i.e., the possibility that children with small lungs are more susceptible to respiratory infections in the first place) cannot be ruled out. Interestingly, the majority of participants with young spirometric restriction who were underweight in ECRHS1 moved to a higher BMI category at follow-up. However, the young onset spirometric pattern was still associated with a prevalence of low fat-free mass that was twice as high as that of the normal pattern.

Obesity, on the contrary, is a known risk factor for the restrictive spirometric pattern and lower FVC levels in older adults, possibly through fat-induced inflammation, altered respiratory mechanics, and/o reduced physical activity.[20, 23] In our study, while BMI showed a U-shaped relation to the young spirometric restriction with both the underweight and obese categories being at increased risk, BMI was linearly associated with the mid-adult onset spirometric restriction with only obese individuals being at increased risk. Most importantly,

the increase in BMI over the years was a strong predictor for mid-adult onset spirometric restriction.

The main limitations of our analysis are that, as in all longitudinal studies with long follow-up periods, we cannot discard the possibility of attrition bias. Most risk factors were assessed using questionnaires and early life factors were assessed retrospectively, which are likely subject to some misclassification. Pre-bronchodilator spirometry was used, therefore participants with obstructive patterns could have had either irreversible or reversible obstruction. One recent study showed that risk factors for the two phenotypes can be different.[27] However, in previous studies risk factors for young spirometric restriction were confirmed after removing individuals with bronchodilator response.[19] We also acknowledge that our study could not differentiate participants with true lung restriction (which needs measurement of total lung capacity) from those with spirometric restriction alone. Spirometric restriction could occur for air trapping and other reasons not necessarily related to lung impairment (among which comorbidities, pain, poor physical conditions etc). However, even when true restriction is absent, the reasons for low FVC should be determined.[2, 3] Likewise, our study was not designed to describe the natural course of abnormal spirometric patterns (i.e. how individuals with young/mid-adult onset evolved over time). Future studies should look into this to understand the natural history of individuals with young abnormal spirometry as they age.

Among the strengths of this study, ECRHS is a large longitudinal population-based cohort that has a long follow-up (>20-years) and is representative of the general population in Europe. This study is the first one to look at distinct trajectories at young and older ages, filling the gap between studies looking at spirometric patterns in younger or older individuals only. We provided a series of sensitivity analysis to ensure that our results were robust to the chosen definition of spirometric patterns and to the inclusion of asthmatics and additional subjects with respiratory symptoms at baseline. Obesity, one of the main determinants of spirometric patterns, was assessed using different measures (clinically measured weight and height (BMI), body-silhouettes, and fat mass) and at different times giving more comprehensive results and providing insight into the temporal sequence of exposures and outcomes.

In conclusion, in a large longitudinal study across Europe, we found that characteristics and risk factors for restrictive and obstructive spirometric patterns differ profoundly based on whether their onset occurs in young versus mid-adult life. Being underweight in childhood and young adult-life was strongly associated with the occurrence of the young spirometric restrictive pattern, while asthma was the main risk factor for the young obstructive pattern. In contrast, adult life risk factors, especially smoking and obesity (and weight gain), were associated with mid-adult onset patterns (obstructive and restrictive, respectively). To be fully effective, prevention efforts will need to target both fostering lung function development in childhood and reducing lung function decline in adult life. In this context, identifying specific, abnormal lung function trajectories will be critical to understand and disentangle the best windows of opportunity to prevent future lung impairments and diseases.

Authors' contributions

Study concept and design: SG, JMA, AEC. Data collection and coordination: SA, SDC, BL, LC, SC, PD, BF, TG, AGC, CJ, RJ, JMM, DN, LPG, IP, NPH, CR, GS, CS, KT, IU, IH, JMA, JGA, DJ. Analysis and interpretation of data: AEC, MH, SDC, SG. Drafting of the manuscript: AEC, SG. Critical revision of the manuscript for important intellectual content: all authors.

Conflicts of interest

Authors have no conflicts of interest

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473 the Supplementary Appendix 1.

Table 1. Participant characteristics in mid-adult life (i.e., as assessed at the ECRHS3 survey) according to spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P*-val**
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Age, mean (sd)	50·4 (5·4)	*49·7 (5·4)	*51·2 (5·2)	50·2 (5·5)	50·9 (5·5)	0·003
Sex, Female	1,277 (55·7%)	184 (49·6%)	159 (52·8%)	105 (56·1%)	178 (50·9%)	0·121
Education						0·141
Low	166 (7·4%)	19 (5·2%)	26 (9·3%)	13 (7·3%)	38 (11·2%)	
Medium	764 (34·3%)	129 (35·6%)	102 (36·4%)	68 (38·0%)	108 (31·8%)	
High	1,3 (58·3%)	214 (59·1%)	152 (54·3%)	98 (54·7%)	194 (57·1%)	
BMI		*	*	*		<0·001
Low	85 (3·7%)	21 (5·7%)	20 (6·7%)	3 (1·6%)	12 (3·4%)	
Normal	833 (36·5%)	128 (34·7%)	94 (31·3%)	36 (19·6%)	133 (38·2%)	
Overweight	923 (40·5%)	130 (35·2%)	105 (35·0%)	66 (35·9%)	143 (41·1%)	
Obese	439 (19·3%)	90 (24·4%)	81 (27·0%)	79 (42·9%)	60 (17·2%)	
Fat-Free Mass (Z-score) ‡		*	*	*		<0·001
Low	87 (5·1%)	29 (10·2%)	14 (6·6%)	5 (4·2%)	20 (7·2%)	
Normal	1,478 (86·8%)	228 (80·3%)	171 (80·7%)	90 (75·0%)	242 (87·1%)	
High	137 (8·0%)	27 (9·5%)	27 (12·7%)	25 (20·8%)	16 (5·8%)	
Fat Mass (Z-score) ‡			*	*		<0·001
Low	107 (6·3%)	17 (6·0%)	21 (9·9%)	4 (3·3%)	11 (4·0%)	
Normal	1,461 (85·8%)	236 (83·1%)	167 (78·8%)	84 (70·0%)	241 (86·7%)	
High	134 (7·9%)	31 (10·9%)	24 (11·3%)	32 (26·7%)	26 (9·4%)	
Smoking status					*	<0·001

Never	1,028 (45·0%)	175 (47·6%)	127 (42·3%)	87 (46·5%)	109 (31·3%)	
Ex-smoker	803 (35·2%)	115 (31·3%)	113 (37·7%)	65 (34·8%)	113 (32·5%)	
Current smoker	453 (19·8%)	78 (21·2%)	60 (20·0%)	35 (18·7%)	126 (36·2%)	
Pack-years, median (IQR)	0·1 (14·0)	0 (19·0)	0·6 (17·0)	0 (16·5)	*12·9 (30·0)	<0·001
Among smokers, median (IQR)	14 (19·5)	*18·9 (24·3)	17·0 (24·0)	16·7 (20·5)	*24·0 (23·0)	<0·001
Asthma last 12mo.	163 (7·1%)	*53 (14·4%)	*103 (34·3%)	12 (6·5%)	*64 (18·7%)	<0·001
Wheezing last 12 mo.	493 (21·5%)	*120 (32·3%)	*150 (49·8%)	*50 (26·7%)	*124 (35·4%)	<0·001
Dyspnea last 12 mo.	76 (3·3%)	*23 (6·2%)	*27 (9·0%)	*13 (7·0%)	16 (4·6%)	<0·001
Chronic bronchitis	105 (5·0%)	25 (7·1%)	*36 (14·5%)	12 (7·0%)	*33 (9·8%)	0·165
Comorbidities						
Heart disease	36 (1·7%)	9 (2·6%)	6 (2·4%)	6 (3·5%)	*14 (4·2%)	0·040
Hypertension	395 (17·3%)	72 (19·5%)	54 (18·0%)	*54 (29·2%)	67 (19·3%)	0·002
Stroke	13 (0·6%)	4 (1·1%)	2 (0·7%)	*6 (3·2%)	2 (0·6%)	0·003
Diabetes	67 (3·2%)	*21 (6·0%)	12 (4·8%)	*15 (8·7%)	*19 (5·7%)	0·001
Depression	352 (15·4%)	68 (18·5%)	57 (19·1%)	36 (19·5%)	68 (19·5%)	0·104
†Ank spondylitis/psoariatic arthr.	39 (1·9%)	12 (3·4%)	4 (1·6%)	*12 (6·9%)	11 (3·3%)	<0·001
Low physical activity#	574 (33·9%)	113 (38·8%)	60 (30·8%)	*60 (42·6%)	85 (34·0%)	0·094

sd: standard deviation. BMI: Body Mass Index. IQR: Interquartile Range. mo:month. *P* -value from chi^2 test (categorical), Kruskal Wallis test (continuous) * *P*-value <0·05 when comparing the corresponding spirometry pattern to the normal pattern. †ankylosing spondylitis or psoariatic arthritis ‡ low if z-score< 10^{th} percentile, high if z-score> the 90^{th} percentile #physical activity was defined as the lowest tertile of total Mets per week.

Table 2. Risk factors distribution according to spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P-value***
	No. %	% No.	No. %	% No.	No. %	
Early-life risk factors						
Maternal age at birth						0·756
≤25 years	672 (34·1%)	100 (33·3%)	91 (38·7%)	57 (37·7%)	102 (34·1%)	
26-31 years	697 (35·4%)	103 (34·3%)	81 (34·5%)	50 (33·1%)	97 (32·4%)	
≥32 years	599 (30·4%)	97 (32·3%)	63 (26·8%)	44 (29·1%)	100 (33·4%)	
Mother education						0·964
Minimum school leaving age	1,353 (65·5%)	227 (66·2%)	164 (67·2%)	115 (68·0%)	215 (65·5%)	
Secondary school past min age	453 (21·9%)	80 (23·3%)	54 (22·1%)	35 (20·7%)	71 (21·6%)	
College or university	260 (12·6%)	36 (10·5%)	26 (10·7%)	19 (11·2%)	42 (12·8%)	
Father education						0·329
Minimum school leaving age	1,121 (55·0%)	169 (50·4%)	129 (54·0%)	85 (51·5%)	167 (51·9%)	
Secondary school past min age	526 (25·8%)	86 (25·7%)	57 (23·8%)	46 (27·9%)	98 (30·4%)	
College or university	393 (19·3%)	80 (23·9%)	53 (22·2%)	34 (20·6%)	57 (17·7%)	
Smoking pregnancy						0·738
No	1,723 (76·0%)	276 (76·0%)	225 (75·5%)	133 (71·5%)	263 (76·5%)	
During childhood	416 (18·3%)	67 (18·5%)	59 (19·8%)	44 (23·7%)	67 (19·5%)	
During pregnancy	129 (5·7%)	20 (5·5%)	14 (4·7%)	9 (4·8%)	14 (4·1%)	
Parental smoking status						0·918
None	678 (30·7%)	117 (33·2%)	88 (30·2%)	57 (32·0%)	98 (28·9%)	

1 parent smoked	1,127 (51·1%)	175 (49·7%)	144 (49·5%)	85 (47·8%)	178 (52·5%)	
2 parents smoked	400 (18·1%)	60 (17·0%)	59 (20·3%)	36 (20·2%)	63 (18·6%)	
Maternal asthma	121 (5·3%)	28 (7·5%)	*30 (10·1%)	14 (7·6%)	*34 (9·9%)	0·001
Paternal asthma	186 (8·3%)	34 (9·3%)	*44 (15·1%)	18 (10·2%)	37 (10·7%)	0·004
Delivered by Caesarean section	71 (3·1%)	10 (2·7%)	12 (4·0%)	6 (3·3%)	5 (1·5%)	0·406
Living place <5 years old						0·078
Farm/rural	628 (32·0%)	88 (29·5%)	66 (27·8%)	40 (26·5%)	98 (32·3%)	
Small town	405 (20·6%)	44 (14·8%)	43 (18·1%)	27 (17·9%)	59 (19·5%)	
Suburb/city	930 (47·4%)	*166 (55·7%)	128 (54·0%)	84 (55·6%)	146 (48·2%)	
Childhood asthma[†]	86 (3·8%)	18 (4·9%)	*43 (14·3%)	7 (3·7%)	*24 (6·9%)	<0·001
Respiratory Infection before 5 years	209 (9·7%)	*47 (13·6%)	*51 (18·4%)	17 (9·8%)	42 (13·0%)	<0·001
Body silhouette at 8 years		*				0·006
1	931 (48·4%)	183 (58·5%)	121 (51·9%)	66 (42·6%)	161 (51·1%)	
2	386 (20·1%)	54 (17·3%)	40 (17·2%)	40 (25·8%)	64 (20·3%)	
3	284 (14·8%)	26 (8·3%)	27 (11·6%)	21 (13·5%)	42 (13·3%)	
4	172 (8·9%)	23 (7·3%)	20 (8·6%)	9 (5·8%)	16 (5·1%)	
5 to 9	151 (7·8%)	27 (8·6%)	25 (10·7%)	19 (12·3%)	32 (10·2%)	
Body silhouette at puberty						0·059
1	361 (21·0%)	81 (27·2%)	55 (26·3%)	19 (14·1%)	67 (23·0%)	
2	610 (35·5%)	102 (34·2%)	73 (34·9%)	49 (36·3%)	104 (35·7%)	
3	383 (22·3%)	48 (16·1%)	35 (16·7%)	37 (27·4%)	61 (21·0%)	
4	233 (13·5%)	41 (13·8%)	25 (12·0%)	15 (11·1%)	30 (10·3%)	
5 to 9	133 (7·7%)	26 (8·7%)	21 (10·0%)	15 (11·1%)	29 (10·0%)	

Young adult life risk factors						
Body silhouette at 30 years		*		*	*	<0·001
1	63 (3·3%)	24 (7·5%)	13 (5·6%)	3 (1·9%)	13 (4·2%)	
2	375 (19·4%)	48 (15·1%)	48 (20·7%)	20 (12·7%)	85 (27·2%)	
3	690 (35·6%)	108 (34·0%)	75 (32·3%)	45 (28·7%)	102 (32·6%)	
4	474 (24·5%)	77 (24·2%)	48 (20·7%)	43 (27·4%)	66 (21·1%)	
5 to 9	334 (17·3%)	61 (19·2%)	48 (20·7%)	46 (29·3%)	47 (15·0%)	
BMI at ECRHS1‡		*	*	*		<0·001
Low	284 (12·4%)	80 (21·6%)	50 (16·6%)	19 (10·2%)	55 (15·7%)	
Normal	1,41 (61·5%)	176 (47·6%)	160 (53·2%)	105 (56·1%)	215 (61·4%)	
Overweight	495 (21·6%)	87 (23·5%)	66 (21·9%)	46 (24·6%)	69 (19·7%)	
Obese	102 (4·5%)	27 (7·3%)	25 (8·3%)	17 (9·1%)	11 (3·1%)	
Smoking status at ECRHS1‡		*			*	<0·001
Never	1,025 (46·1%)	178 (50·1%)	119 (42·2%)	88 (48·4%)	102 (29·4%)	
Ex-smoker	430 (19·4%)	49 (13·8%)	57 (20·2%)	34 (18·7%)	62 (17·9%)	
Current smoker	767 (34·5%)	128 (36·1%)	106 (37·6%)	60 (33·0%)	183 (52·7%)	
Pack-years at ECRHS1‡, median (IQR)	0·8 (8·0)	0 (8·0)	*2 (11·5)	0·8 (8· 5)	*5·8 (15·0)	<0·001
Pack-years at ECRHS1‡ in ever smokers, median (IQR)	7·2 (12·7)	8·1 (11·7)	*10·4 (13·0)	8·2 (11·2)	*12 (12·7)	<0·001
Atopy at ECRHS1$	586 (29·3%)	106 (34·0%)	*122 (49·0%)	44 (26·7%)	105 (32·3%)	<0·001
Asthma last 12 months at ECRHS1‡	109 (4·8%)	*31 (8·4%)	*85 (28·4%)	12 (6·4%)	*35 (10·0%)	<0·001

Information for all risk factors was collected at ECRHS1, with the exception of information on body silhouette at 8 years, at puberty and at 30 years, which was recalled at ECRHS3.

sd: standard deviation; IQR: Interquartile Range. *P* -value from chi-squared test (categorical) and Kruskal Wallis test (continuous) * *P*-value <0·05 when comparing corresponding spirometry pattern to the group with normal spirometry after adjustment for age and sex. † Childhood asthma defined as first asthma attack occurring before 11 years old. $ Atopy (yes if at least 1 Spe-IgE was >0·35 ng/ml, measured at ECRHS1)

Table 3. Association between early-life and young adult-life risk factors and spirometric patterns

	Young onset restrictive	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**
	RRR 95%CI	RRR 95%CI	RRR 95%CI	RRR 95%CI
Early-life risk factors				
Maternal asthma	1·48 (0·96-2·28)	**1·77 (1·15-2·72)**	1·46 (0·82-2·59)	**1·84 (1·23-2·76)**
Paternal asthma	1·15 (0·78-1·69)	**1·72 (1·20-2·48)**	1·25 (0·75-2·09)	1·25 (0·85-1·82)
Childhood asthma	1·22 (0·72-2·08)	**3·36 (2·22-5·07)**	0·98 (0·44-2·17)	1·60 (0·99-2·60)
Resp. Infect. <5yrs	**1·48 (1·05-2·08)**	**1·97 (1·40-2·77)**	1·01 (0·60-1·70)	1·34 (0·94-1·92)
Body silhouette at 8yrs†				
1	**1·61 (1·21-2·14)**	1·25 (0·90-1·73)	0·80 (0·55-1·16)	1·04 (0·79-1·37)
2 and 3	1	1	1	1
4	1·12 (0·68-1·84)	1·18 (0·69-2·01)	0·56 (0·27-1·16)	0·59 (0·34-1·04)
5 to 9	1·47 (0·92-2·36)	1·62 (0·98-2·67)	1·40 (0·81-2·42)	1·30 (0·84-2·01)
Young adult risk factors				
Body silhouette at 30yrs†				
1	**2·52 (1·52-4·16)**	1·70 (0·90-3·21)	0·77 (0·23-2·52)	1·11 (0·60-2·06)
2 and 3	1	1	1	1
4	1·11 (0·83-1·50)	0·87 (0·61-1·25)	1·48 (0·99-2·21)	0·80 (0·59-1·08)
5 to 9	1·20 (0·87-1·66)	1·30 (0·90-1·87)	**2·32 (1·55-3·46)**	0·80 (0·57-1·13)
BMI at ECRHS1				
Low	**2·43 (1·80-3·29)**	**1·67 (1·18-2·38)**	0·87 (0·52-1·45)	1·38 (0·99-1·92)
Normal	1	1	1	1
Overweight	**1·37 (1·03-1·82)**	1·06 (0·77-1·45)	1·30 (0·90-1·88)	0·84 (0·63-1·13)
Obese	**2·20 (1·39-3·48)**	**1·81 (1·12-2·93)**	**2·34 (1·34-4·08)**	0·64 (0·34-1·23)
Smoking status at ECRHS1				
Never-smoker	1	1	1	1
Ex-smoker	**0·68 (0·48-0·96)**	1·09 (0·77-1·54)	0·93 (0·61-1·42)	1·40 (1·00-1·98)
Current smoker	0·95 (0·74-1·22)	1·12 (0·84-1·49)	0·91 (0·65-1·28)	**2·32 (1·78-3·01)**
Atopy at ECRHS1	1·20 (0·92-1·60)	**2·14 (1·63-2·83)**	0·89 (0·62-1·28)	1·10 (0·85-1·43)
Asthma last 12 mo. at ECRHS1	**1·84 (1·17-2·89)**	**6·94 (4·81-10·01)**	1·38 (0·71-2·68)	**1·74 (1·12-2·70)**

RRR: Relative Risk Ratio from multinomial logistic regression adjusted for age, sex and symptomatic sample. Centre was included as random effect. The group with normal spirometry was the reference group. 95%CI: 95% confidence interval. Resp. Infect.: history of respiratory infection before 5 years. BMI: Body Mass Index. †recalled at ECRHS3

Table 4. Changes and longitudinal categories of risk factors from young to mid-adult life by spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P-value***
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
BMI longitudinal categories		*	*	*	*	<0·001
Persistent underweight	60 (2·6%)	18 (4·9%)	17 (5·7%)	3 (1·6%)	8 (2·3%)	
Persistent normal weight	632 (27·7%)	75 (20·4%)	64 (21·3%)	24 (13·0%)	87 (25·0%)	
Persistent Overweight/obese	564 (24·8%)	108 (29·3%)	90 (30·0%)	59 (32·1%)	77 (22·1%)	
Underweight to normal	175 (7·7%)	48 (13·0%)	30 (10·0%)	11 (6·0%)	44 (12·6%)	
Underweight/normal to overweight/obese	796 (34·9%)	112 (30·4%)	96 (32·0%)	86 (46·7%)	126 (36·2%)	
Decrease in BMI category	51 (2·2%)	7 (1·9%)	3 (1·0%)	1 (0·5%)	6 (1·7%)	
Δ BMI[†], median (IQR)	2·87 (±3·2)	2·79 (±3·7)	3·01 (±3·9)	*4·72 (±5·3)	2·85 (±3·3)	<0·001
Smoking longitudinal categories					*	<0·001
Never	933 (42·0%)	162 (46·0%)	110 (39·0%)	80 (44·0%)	94 (27·2%)	
Ex-smoker	383 (17·3%)	39 (11·1%)	50 (17·7%)	31 (17·0%)	53 (15·4%)	
Quitters	465 (20·9%)	76 (21·6%)	65 (23·0%)	37 (20·3%)	72 (20·9%)	
Late smokers	78 (3·5%)	13 (3·7%)	9 (3·2%)	6 (3·3%)	11 (3·2%)	
Persistent smokers	361 (16·3%)	62 (17·6%)	48 (17·0%)	28 (15·4%)	115 (33·3%)	
Δ pack-years, median (IQR)[‡]	0 (3·2)	*0 (7·7)	0 (3·0)	0 (3·6)	*0·3 (14·0)	<0·001
Δ pack-years (ever smokers), median (IQR)[‡]	2·2 (11·2)	*6·5 (18·9)	0·9 (10·7)	2·6 (11·0)	*8·8 (17·9)	<0·001

IQR : Interquartile Range. [†]difference between BMI measured at ECRHS3 and ECRHS1· [‡]difference in pack-years of smoking between ECRHS3 and ECRHS1. * *P*-value <0·05 when comparing corresponding spirometric pattern to the group with normal spirometry.

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FIGURES

Figure 1. Flow-chart. Blue boxes refer to the spirometric pattern groups included in analyses.

Figure 2. Predicted mean with 95% Confidence Intervals of FEV_1 (a), FVC (b), and FEV_1/FVC (c) from mixed linear regression models including age, age^2, sex, spirometric trajectories, and their interactions with age.